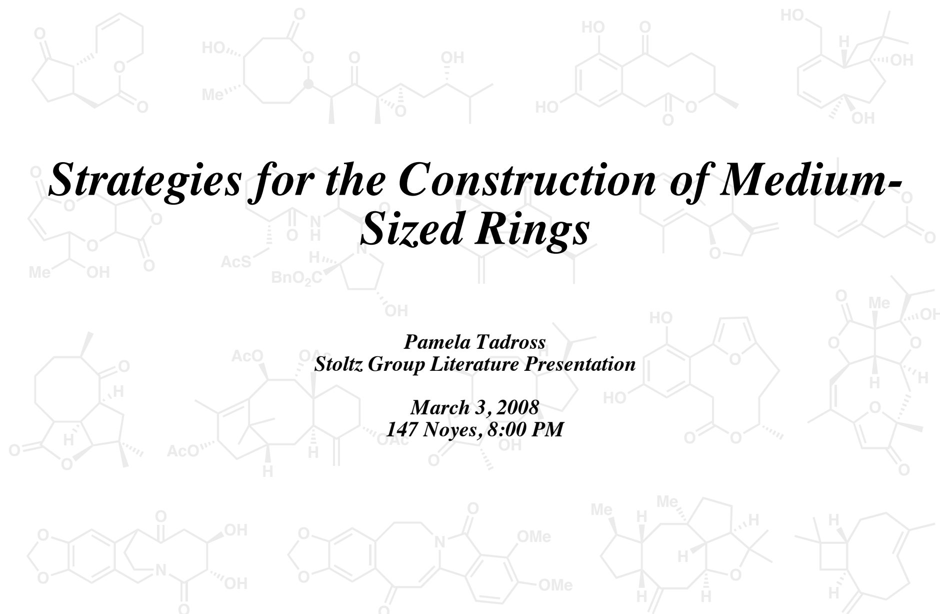
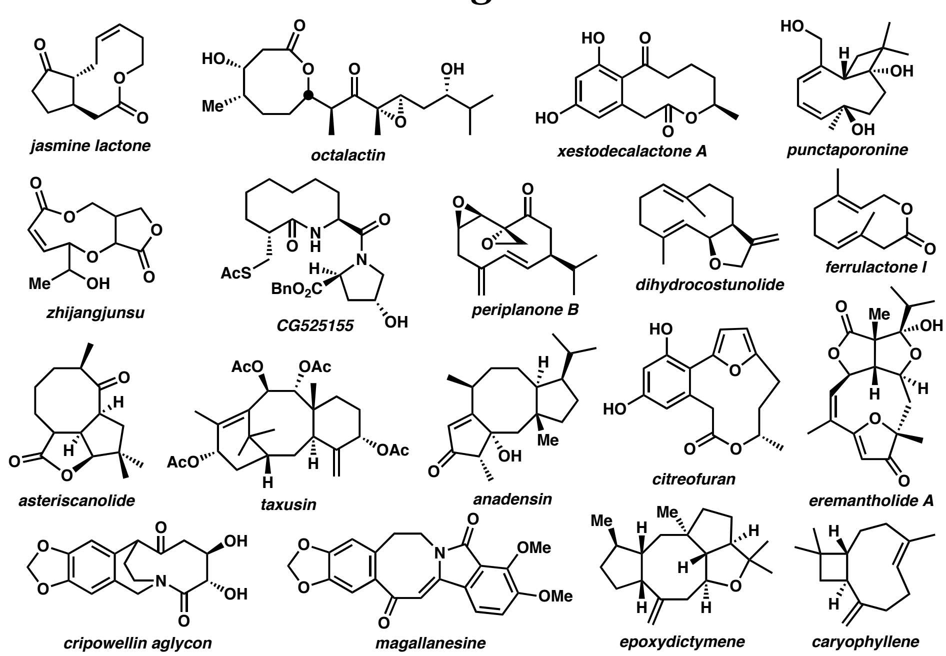


Strategies for the Construction of Medium-Sized Rings

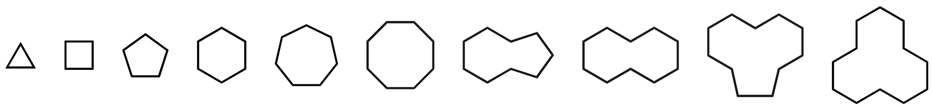
Pamela Tadross
Stoltz Group Literature Presentation

March 3, 2008
147 Noyes, 8:00 PM

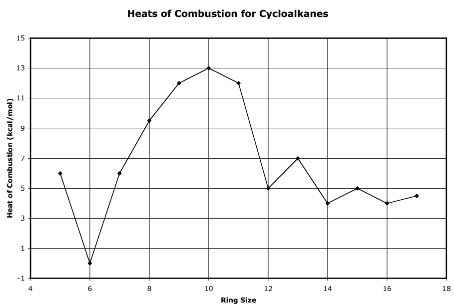
Medium-Sized Ring Natural Products



Classification of Medium-Sized Rings



Medium Rings



Rings containing 12 or more atoms fall into the large ring category.

Rings containing 17 or more atoms are so large they are barely distinguishable from their acyclic analogs.

The Difficulty with Medium-Sized Rings

ENTROPY

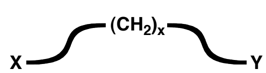
Kinetic Implications:

The probability of an end to end reaction in a bifunctional linear chain molecule decreases as the length of the chain increases

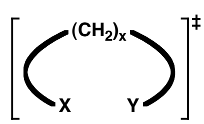
Torsional degrees of freedom are limited by the ring-like transition state for cyclization

Thermodynamic Implications:

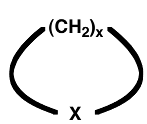
The product cycle limits the number of torsional degrees of freedom between covalently bonded groups compared to the linear chain molecule



Linear Bifunctional Chain Molecule



Ring-like Transition State



Medium-Sized Ring Product

ENTHALPY

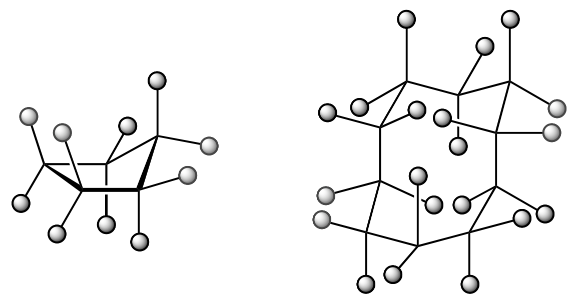
Kinetic Implications:

The activation energy for ring closure reflects the ring strain of the transition state for cyclization

Thermodynamic Implications:

Strain present in the product cycle destabilizes medium-sized rings

Origins of Ring Strain in Medium-Sized Rings

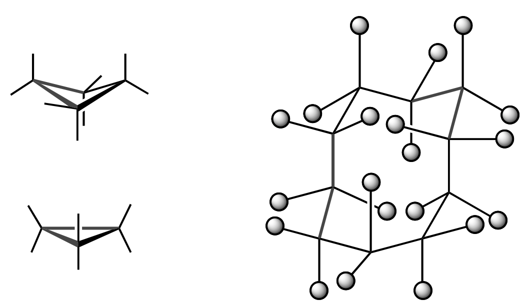


Bond Opposition Forces (also known as Pitzer strain)

The result of unfavorable eclipsing interactions in a given conformation

Dominant source of strain for common rings (5-, 6-, 7-membered rings)

Origins of Ring Strain in Medium-Sized Rings

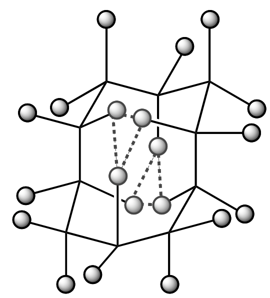


Bond Angle Distortion (also known as Baeyer strain)

Often broken down into two categories: small angle and large angle strain

Dominant source of strain for small rings (3- and 4-membered rings)

Origins of Ring Strain in Medium-Sized Rings



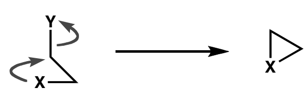
Transannular Orbital Interactions

Often confused with van der Waal radii compression
Results from unfavorable steric interactions between groups that lie across the ring from one another

Cannot be avoided in medium-sized rings without adding severe torsional and bond angle distortion!
Elimination of transannular interactions comes at the cost of minimized Baeyer and Pitzer strains

Entropy vs. Enthalpy

For small ring formations:



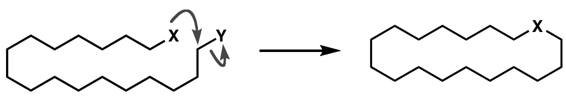
- ***Large enthalpic cost (Pitzer and Baeyer strain) in the transition state and product cycle***
- ***Relatively small entropic cost in the transition state with significant entropic cost in the product cycle due to loss of torsional degrees of freedom***

Entropy vs. Enthalpy

For small ring formations:

- *Large enthalpic cost (Pitzer and Baeyer strain) in the transition state and product cycle*
- *Relatively small entropic cost in the transition state with significant entropic cost in the product cycle due to loss of torsional degrees of freedom*

For large ring formations:



- ***Small enthalpic cost***
- ***Large entropic cost in the transition state but little to no entropic cost in the product cycle***

Entropy vs. Enthalpy

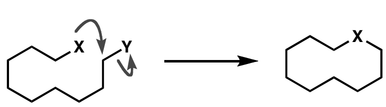
For small ring formations:

- *Large enthalpic cost (Pitzer and Baeyer strain) in the transition state and product cycle*
- *Relatively small entropic cost in the transition state with significant entropic cost in the product cycle due to loss of torsional degrees of freedom*

For large ring formations:

- *Small enthalpic cost*
- *Large entropic cost in the transition state but little to no entropic cost in the product cycle*

For medium ring formations:



- ***Very large enthalpic cost due to transannular interactions in the transition state and product***
- ***Substantial entropic cost in the transition state with smaller entropic costs in the product cycle***

Quantitative Evaluation of Cyclization Reactions: Effective Molarity

Effective Molarity (EM): Quantitative measure of the ease of ring closure

For studies of reaction rates:

$$EM = k_{intra}/k_{inter} \qquad (1)$$

For equilibrium studies:

$$EM = K_{intra}/K_{inter} \qquad (2)$$

In case that's not enough math:

$$EM = e^{[-(\Delta H_{intra} - \Delta H_{inter})/RT]} \cdot e^{[(\Delta S_{intra} - \Delta S_{inter})/R]} \qquad (3)$$

ΔH and ΔS should be read as $\Delta H°$ and $\Delta S°$ (equilibrium case) and $\Delta H^{‡}$ and $\Delta S^{‡}$ (rate case)
(derived from applying either TS theory or thermodynamics to Eq. 1 and 2)

But we can make Eq. 3 easier to handle:

$$EM = EM_H \times EM_S \qquad (4)$$

Bottom line: Enthalpy and Entropy independently affect the ease of ring closure

Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125.

Quantitative Evaluation of Cyclization Reactions: Effective Molarity

The EM for a system represents an intramolecular reactivity that has been corrected for the inherent reactivity of the end groups

Just a few comments on Eq. 3:

$$EM = e^{[-(\Delta H_{intra} - \Delta H_{inter})/RT]} \cdot e^{[(\Delta S_{intra} - \Delta S_{inter})/R]} \qquad (3)$$

$(\Delta H°_{intra} - \Delta H°_{inter})$ = strain energy of the ring

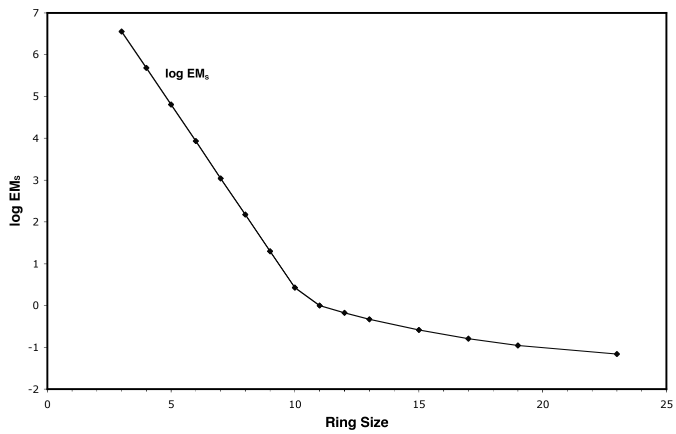
$(\Delta H^{‡}_{intra} - \Delta H^{‡}_{inter})$ = strain energy of the ring-shaped TS

$(\Delta S_{intra} - \Delta S_{inter})$ depends solely on the number of skeletal bonds in the bifunctional precursor undergoing cyclization

Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125.

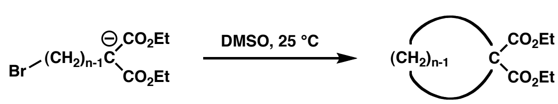
Quantitative Evaluation of Cyclization Reactions: Effective Molarity

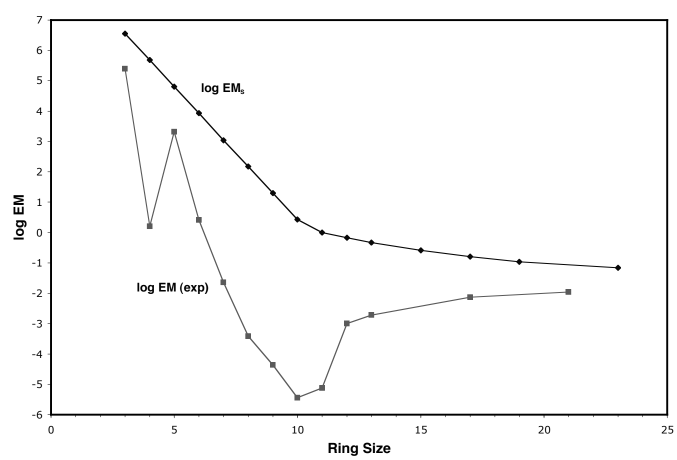
(ΔS_{intra} – ΔS_{inter}) depends solely on the number of skeletal bonds in the bifunctional precursor undergoing cyclization



Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125.

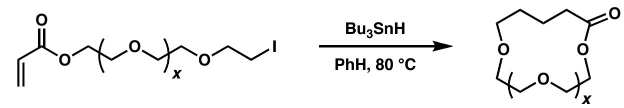
Quantitative Evaluation of Cyclization Reactions: Effective Molarity

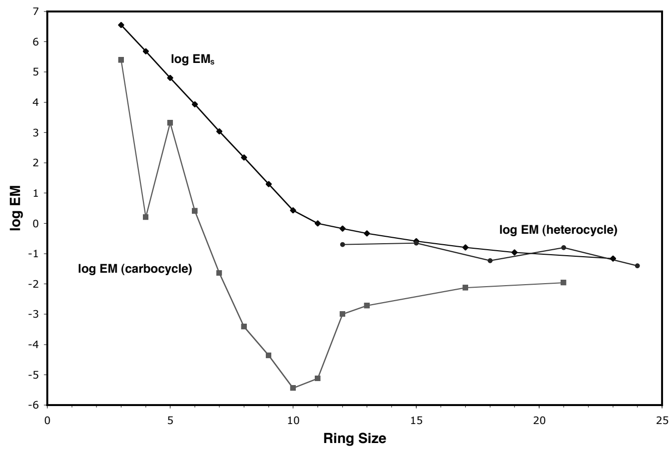




Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125.

Alleviating Strain: Heteroatom Effects

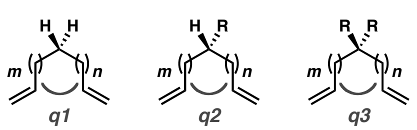




Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125.

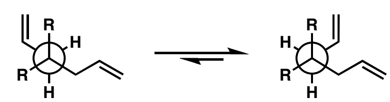
Overcoming Entropy: The Thorpe-Ingold and Gem-Dialkyl Effects

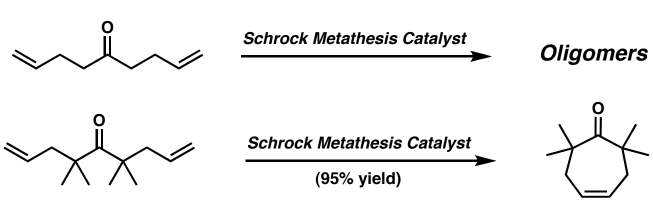
Thorpe-Ingold Effect



q1 > q2 > q3

Gem-Dialkyl Effect

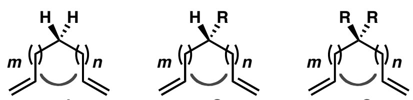




Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041.

Overcoming Entropy: The Thorpe-Ingold and Gem-Dialkyl Effects

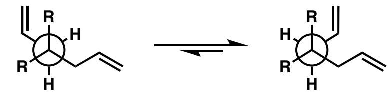
Thorpe-Ingold Effect



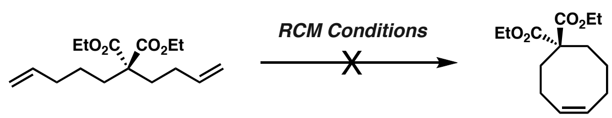
q1 *q2* *q3*

q1 > q2 > q3

Gem-Dialkyl Effect



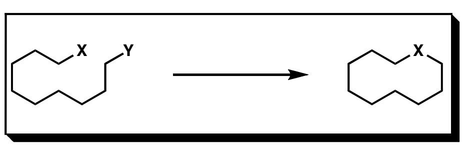
anti *gauche*



Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

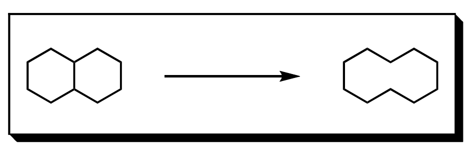
Strategies for the Synthesis of Medium-Sized Rings

Macrocyclization Reactions



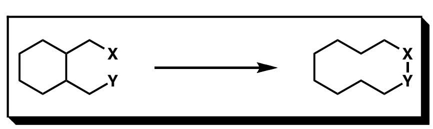
including carbocyclizations, macrolactonizations, and macrolactamizations

Fragmentation Reactions



including ionic and radical processes

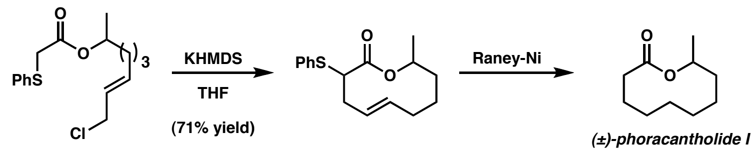
Ring Expansion (and Contraction) Reactions



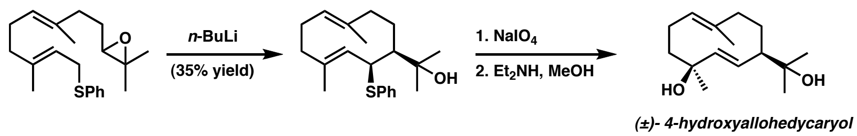
including pericyclic methods

Macrocyclization Methods

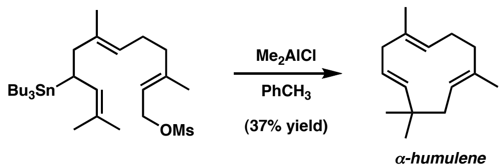
Alkylation of Stabilized Anions



Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424.



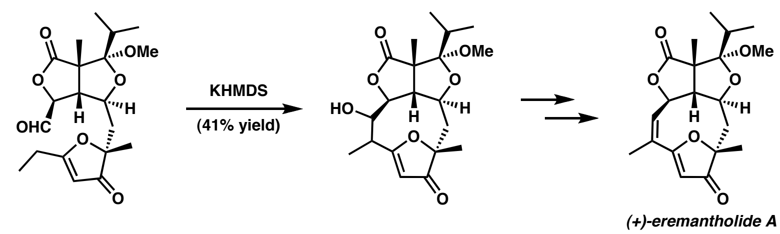
Kodama, M.; Shimada, K.; Takahashi, T.; Kabuto, C.; Itô, S. *Tetrahedron Lett.* **1981**, *22*, 4271-4274.



Corey, E. J.; Daigneault, S.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3675-3678.

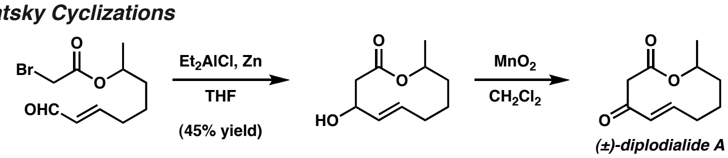
Macrocyclization Methods

Aldol Condensation



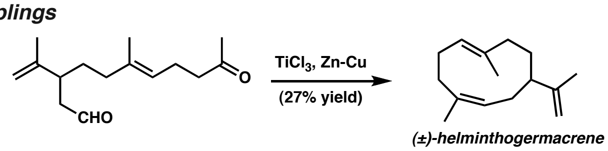
Takao, K.; Ochiai, H.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179-8193.

Reformatsky Cyclizations



Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1978**, 1817.

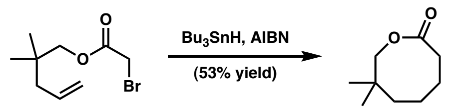
Carbonyl Couplings



McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1985**, *26*, 2171-2172.

Macrocyclization Methods

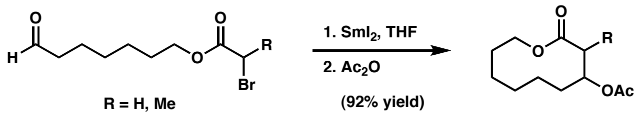
Radical Cyclizations



9 examples

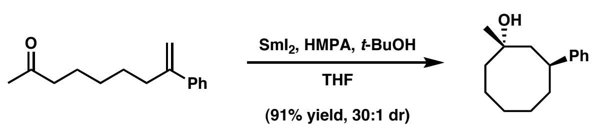
25-53% yield

Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981-10982.



9- and 11-membered rings form in >76% yield

Tabuchi, T.; Kawamura, K.; Inanga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.

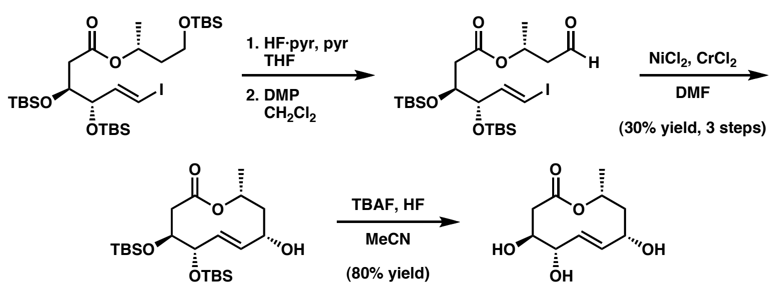


17 examples

24-91% yield

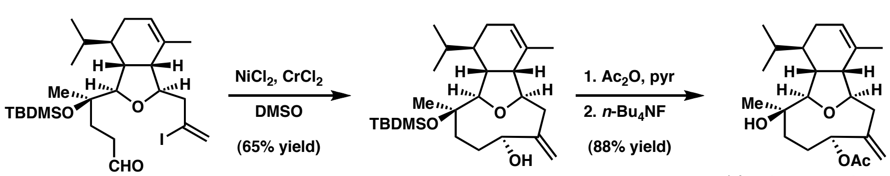
Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186.

Macrocyclization Methods: The Nozaki-Hiyama-Kishi Reaction



(–)-decarestrictine D

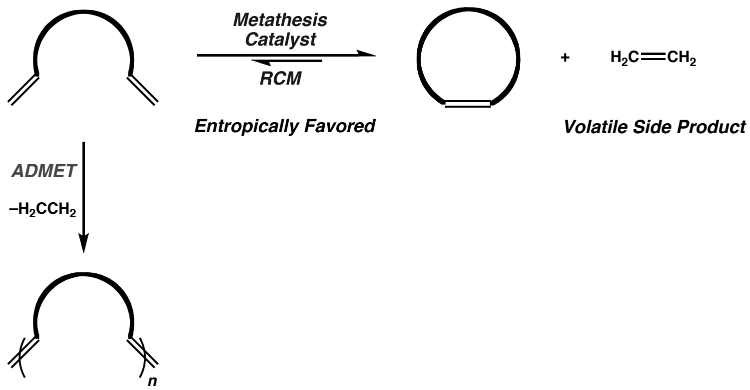
Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421.



(–)-7-deacetoxyalcyonin acetate

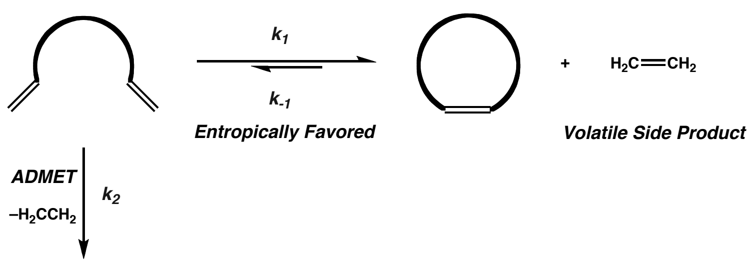
MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

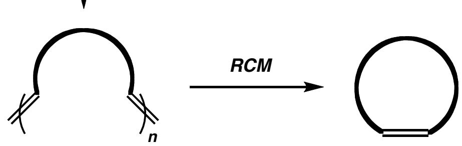
Macrocyclization Methods: Ring-Closing Metathesis



Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285-299.

Macrocyclization Methods: Ring-Closing Metathesis

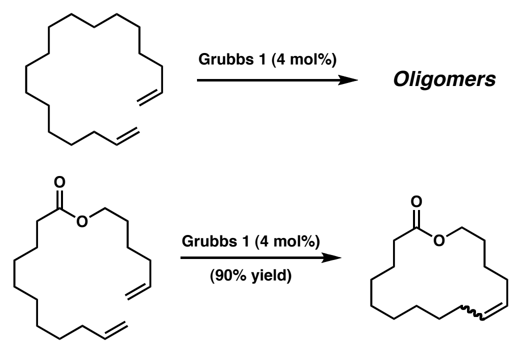


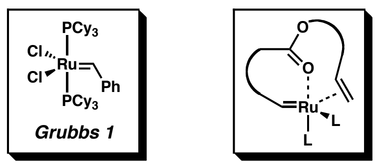


- ***k_1 and k_2 are controlled by adjusting the dilution of the reaction***
- ***RCM vs. ADMET depends on the ring size formed, conformational bias of the substrate, catalyst used, and functional groups present in the substrates***

Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285-299.

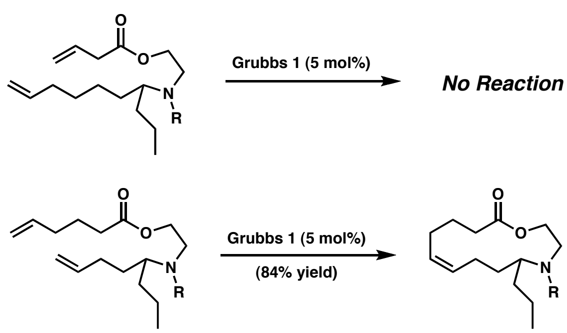
RCM: Heteroatom Effects

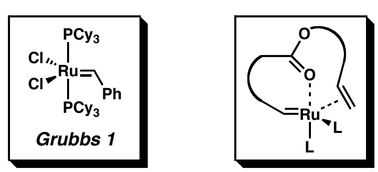




Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285-299.

RCM: Site of Ring Closure

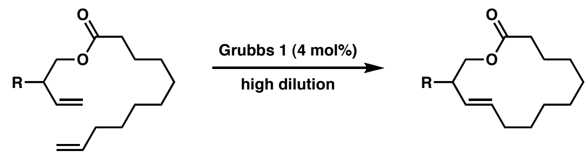




Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285-299.

RCM: Substituent Effects

Allylic Substitution

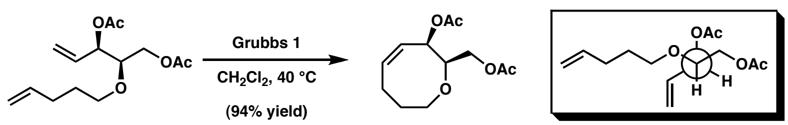


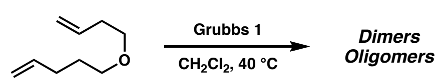
R = H (52% yield)

R = Me (10% yield)

Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285-299.

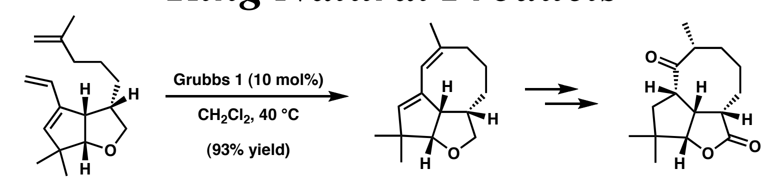
Gauche Effects





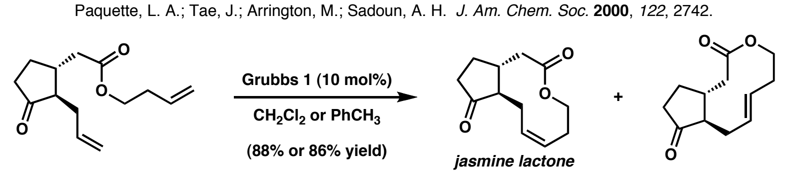
Maier, M. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073-2077.

RCM in the Total Synthesis of Medium-Sized Ring Natural Products



(+)-asteriscanolide

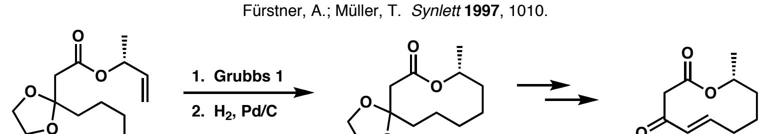
Paquette, L. A.; Tae, J.; Arrington, M.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742.



jasmine lactone

Z **:** ***E*** **= 1.4 : 1 (CH_2Cl_2)**
Z **:** ***E*** **= 2.5 : 1 ($PhCH_3$)**

Fürstner, A.; Müller, T. *Synlett* **1997**, 1010.

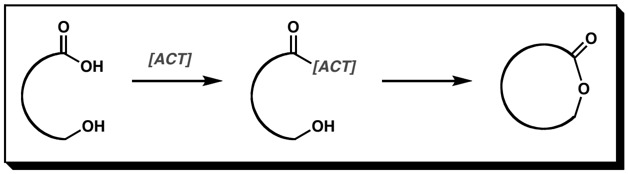


(+)-diplodialide A

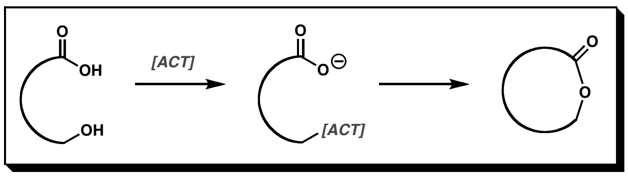
Anand, R. V.; Baktharaman, S.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 3356.

Macrolactonization Methods

Acid Activation



Alcohol Activation

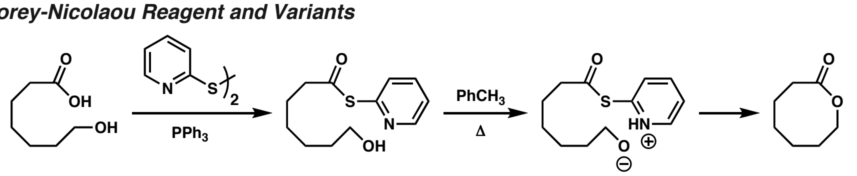


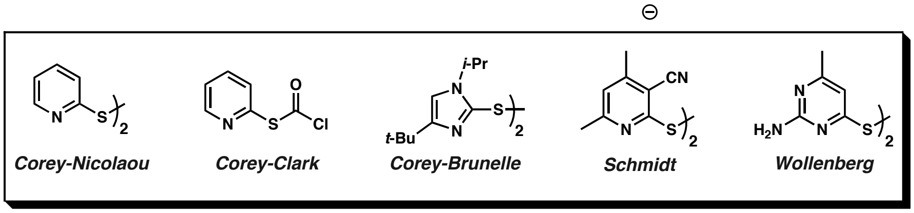
Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911-939.

Macrolactonization Methods

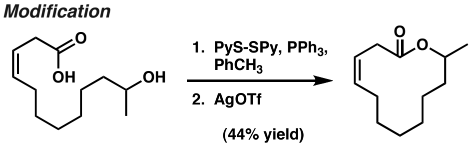
Acid Activation

Corey-Nicolaou Reagent and Variants





Gerlach Modification



ferrulactone II

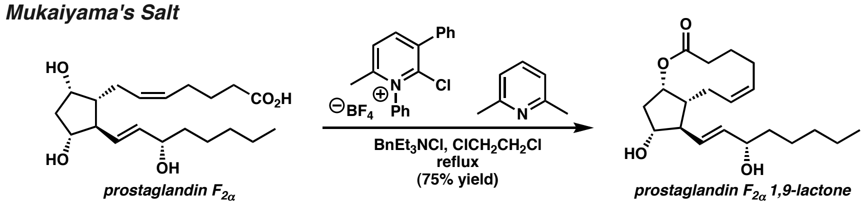
Corey-Brunelle: No Reaction

Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911-939.

Macrolactonization Methods

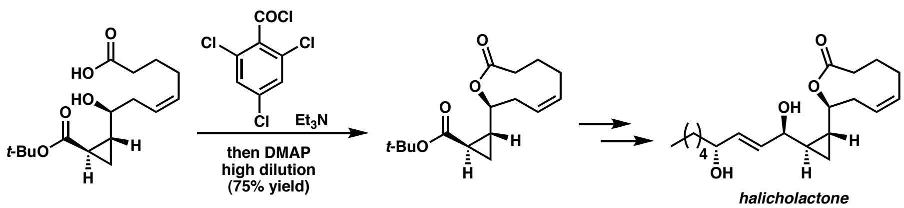
Acid Activation

Mukaiyama's Salt



Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885-888.

Yamaguchi-Yonemitsu



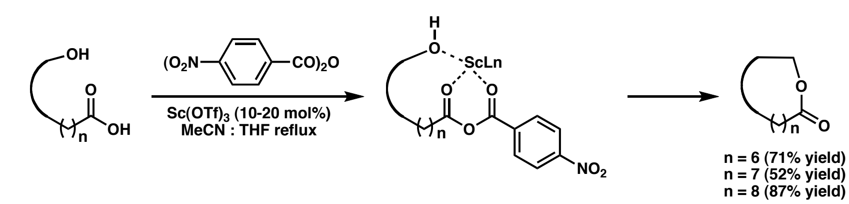
Yonemitsu Conditions: Acid chloride, base and DMAP in one pot

Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911-939.

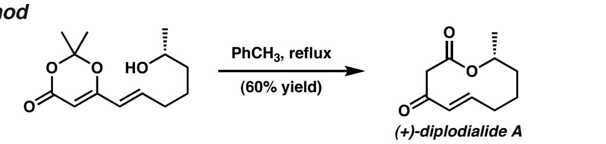
Macrolactonization Methods

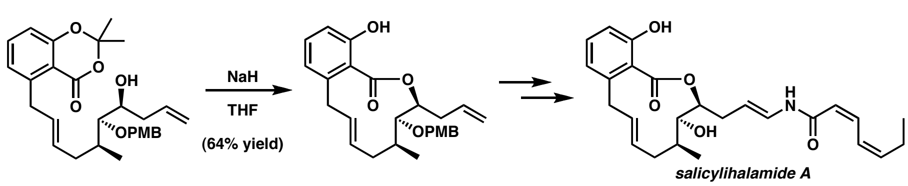
Acid Activation

Yamamoto Lactonization



Boeckman's Method



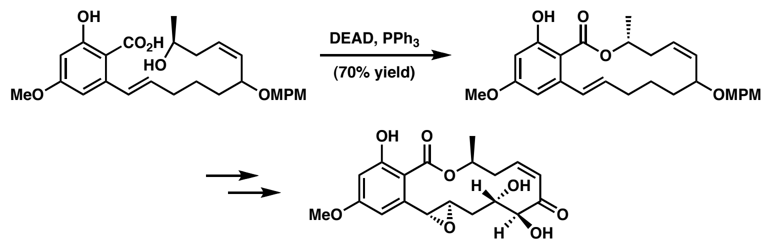


Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911-939.

Macrolactonization Methods

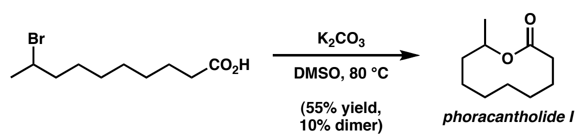
Alcohol Activation

Mitsunobu Reactions



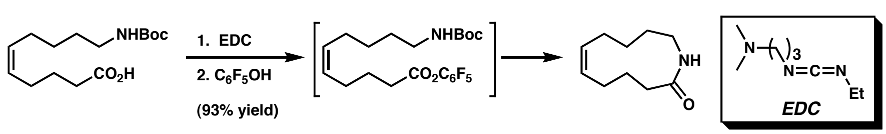
hypothemycin

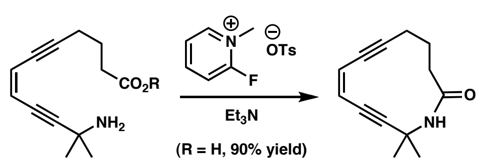
S_N2 Displacements of Mesylates and Halides



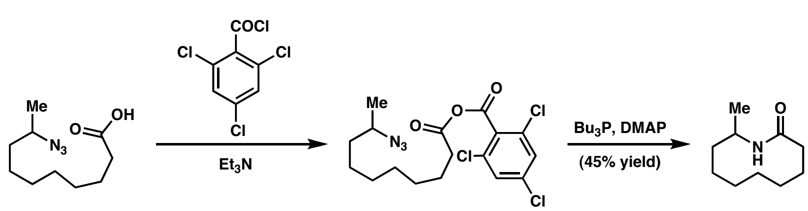
Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911-939.

Macrolactamization Methods





For R = Me, Me_3Al in CH_2Cl_2, 72% yield



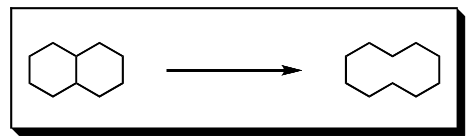
Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125-196.

Strategies for the Synthesis of Medium-Sized Rings

Macrocyclization Reactions

including carbocyclizations, macrolactonizations, and macrolactamizations

Fragmentation Reactions



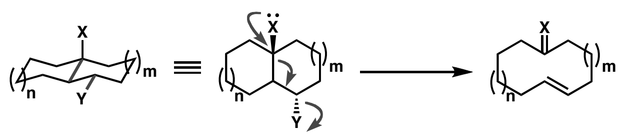
including ionic and radical processes

Ring Expansion (and Contraction) Reactions

including pericyclic methods

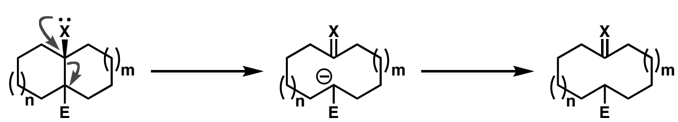
The Grob and Wharton Fragmentations

The Wharton Fragmentation

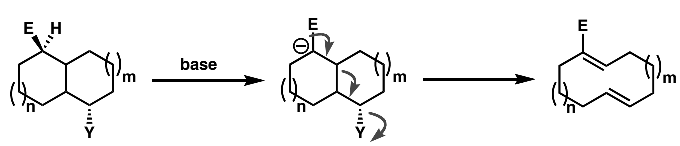


Y = OSO_2R, Cl, Br, I
X = OH, NR_2, CH_2MgBr

Grob-Type Fragmentations

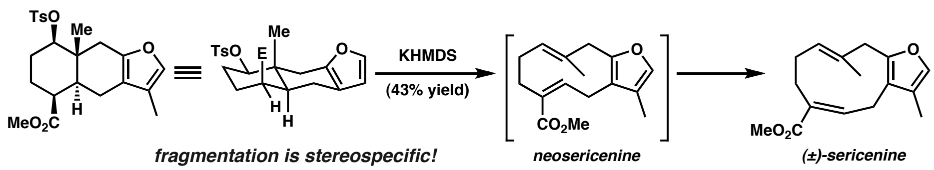


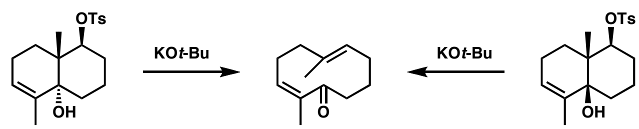
E = anion-stabilizing or electron-withdrawing group



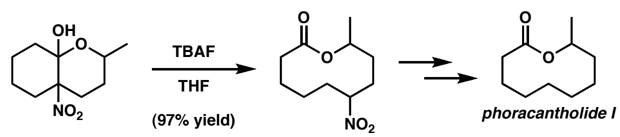
The Grob and Wharton Fragmentations

Synthetic Examples





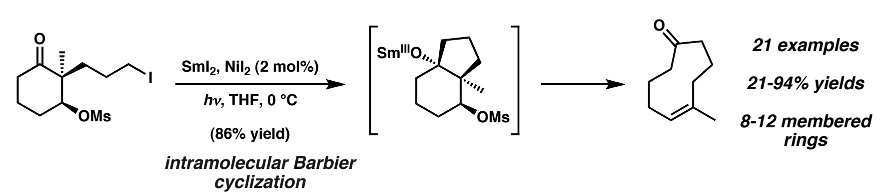
Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115-2146.



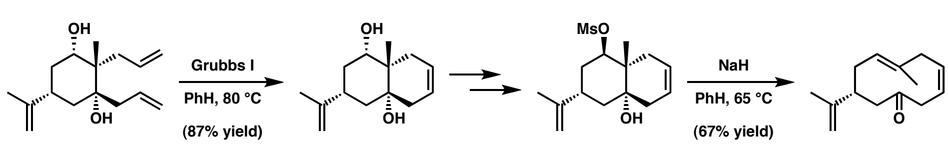
Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S., Jr. *Synthesis* **2007**, *21*, 3261-3285.

The Grob and Wharton Fragmentations

Synthetic Examples

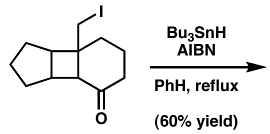


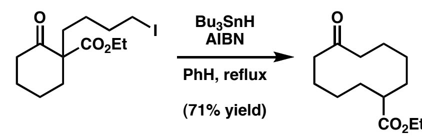
Molander, G. A.; Le Huérou, Y.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511-4516.



Mehta, G.; Kumaran, R. S. *Tetrahedron Lett.* **2005**, *46*, 8831-8835.

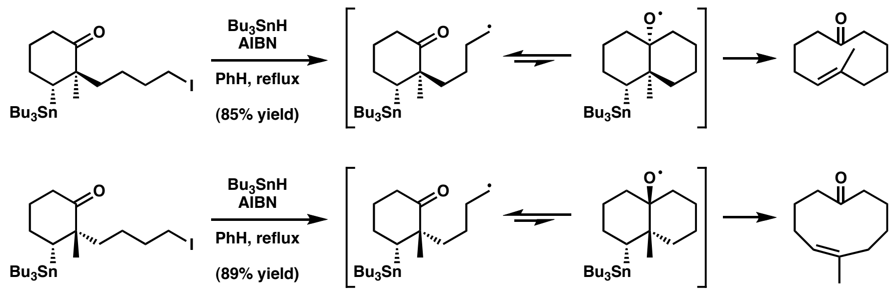
Radical Fragmentation Methods





Lange, G. L.; Gottardo, C. *Tetrahedron Lett.* **1990**, *31*, 5985-5988.

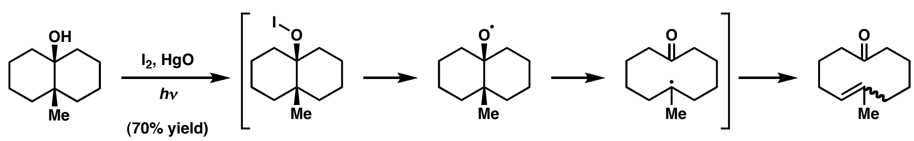
Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548-6549.



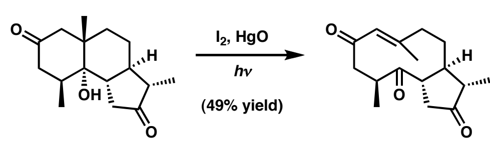
stereospecificity indicative of a concerted fragmentation process

Baldwin, J. E.; Adlington, R. M.; Robertson, J. *J. Chem. Soc. Chem. Commun.* **1988**, 1404-1406.
Baldwin, J. E.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909-922.

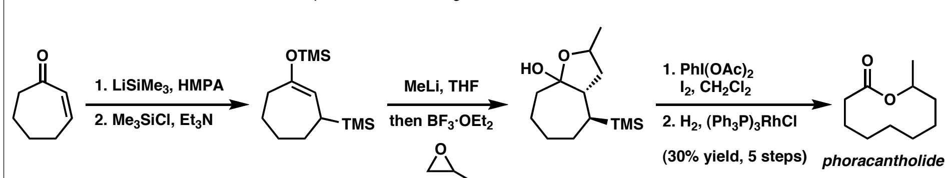
Radical Fragmentation Methods



Suginome, H.; Kondoh, T.; Gogonea, C.; Singh, V.; Hoto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 69-81.

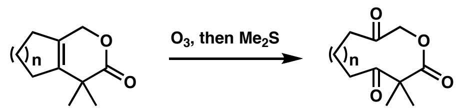


Harapanhalli, R. S. *Liebigs Ann. Chem.* **1988**, 1009-1011.



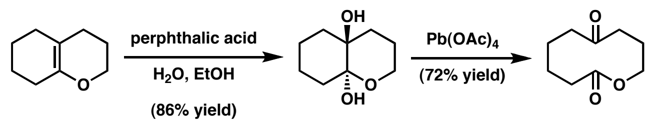
Hatcher, M. A.; Borstnik, K.; Posner, G. H. *Tetrahedron Lett.* **2003**, *44*, 5407.

Miscellaneous Fragmentation Methods

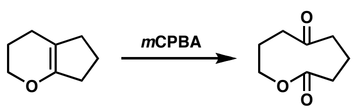


n = 1 (62% yield)
n = 2 (51% yield)
n = 3 (50% yield)

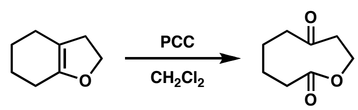
Falbe, J.; Korte, F. *Chem. Ber.* **1963**, *96*, 919.



Borowitz, I. J.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G. J. *J. Org. Chem.* **1966**, *31*, 3032.



9-10 membered rings, 50-90% yield



8-12 membered rings, 63-85% yield

Borowitz, I. J.; Rapp, R. *J. Org. Chem.* **1969**, *34*, 1370.

Graffe, B.; Sacquet, M .C.; Maitte, P.
Bull. Soc. Chim. Fr. II **1979**, 350.

Strategies for the Synthesis of Medium-Sized Rings

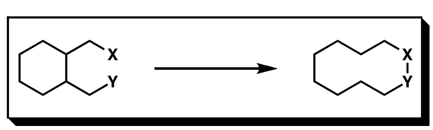
Macrocyclization Reactions

including carbocyclizations, macrolactonizations, and macrolactamizations

Fragmentation Reactions

including ionic and radical processes

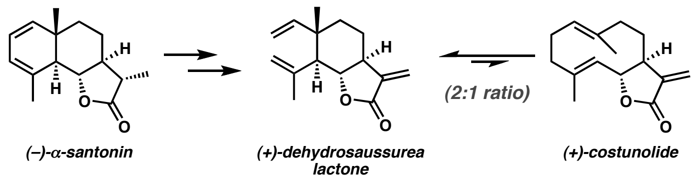
Ring Expansion (and Contraction) Reactions



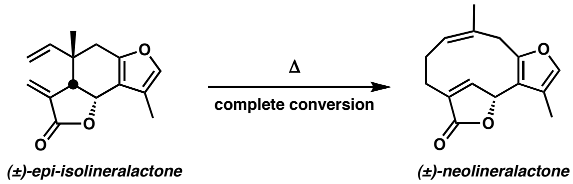
including pericyclic methods

Pericyclic Ring Expansive Processes

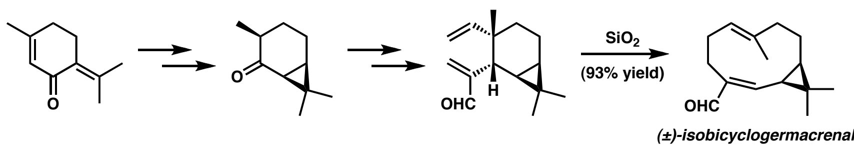
Cope Rearrangements



Grieco, P. A.; Nishazawa, M. *J. Org. Chem.* **1977**, *42*, 1717-1720.



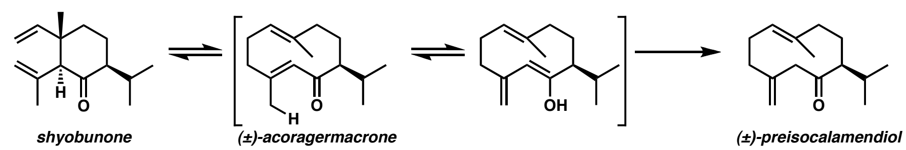
Gopolan, A.; Magnus, P. J. *J. Org. Chem.* **1984**, *49*, 2317-2321.



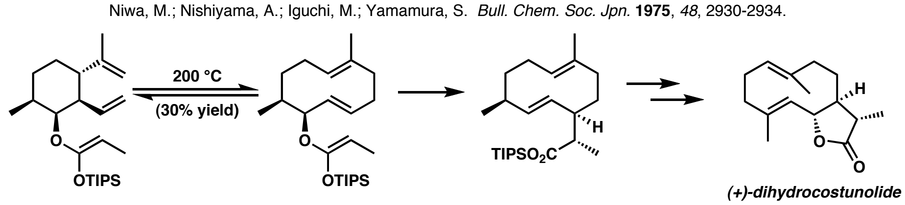
Magari, H.; Hirota, H.; Takahashi, T. *J. Chem. Soc. Chem. Commun.* **1987**, 1196-1198.

Pericyclic Ring Expansive Processes

Tandem Pericyclic Rearrangements

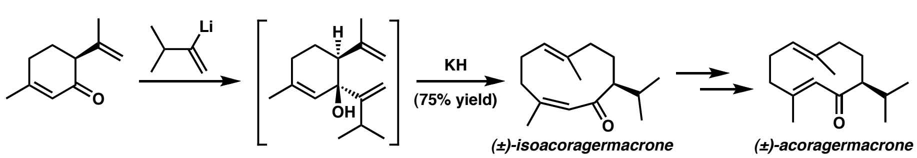


Niwa, M.; Nishiyama, A.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2930-2934.



Raucher, S.; Chi, K.-W.; Hwang, K.-J.; Burks, J. E., Jr. *J. Org. Chem.* **1986**, *51*, 5503-5505.

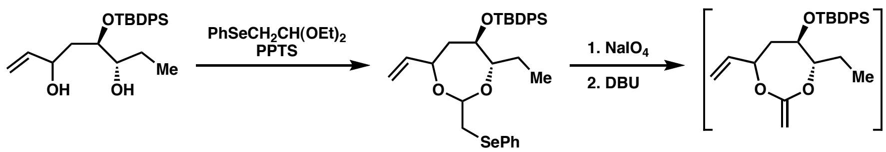
Anionic Oxy-Cope Rearrangements

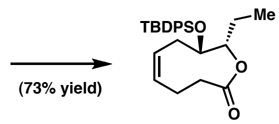


Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186-4187.

Pericyclic Ring Expansive Processes

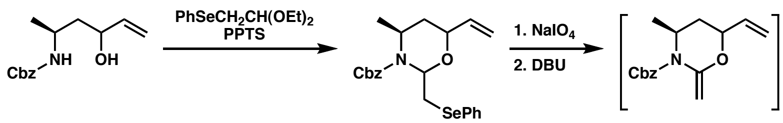
Claisen Rearrangements

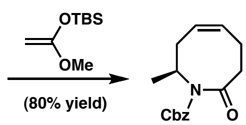




applicable for synthesis of 8-, 9-, and 10-membered lactones

Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron* **1991**, *47*, 7171.



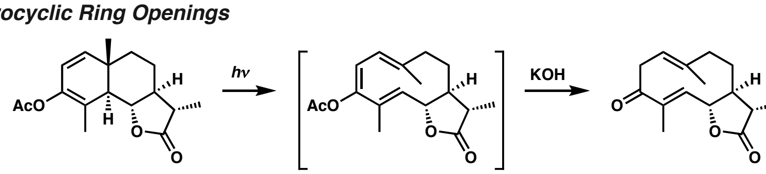


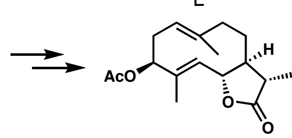
applicable for the synthesis of 7-, 8-, 9-, and 10-membered lactams

Evans, P. A.; Holmes, A. B.; McGeary, R. P.; et al. *J. Chem. Soc. Perkin Trans. 1* **1996**, *1*, 123.

Pericyclic Ring Expansive Processes

Electrocyclic Ring Openings

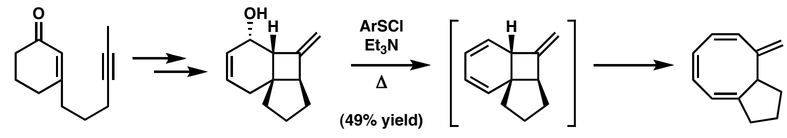




dihydronovanin

no product isolated without in situ saponification

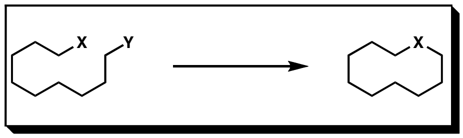
Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc. Chem. Commun.* **1972**, 698.



Wang, T.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 5232.

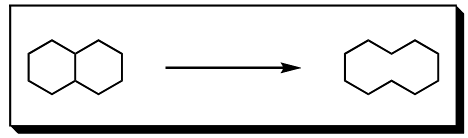
Strategies for the Synthesis of Medium-Sized Rings

Macrocyclization Reactions



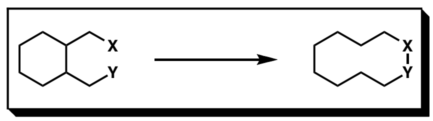
including carbocyclizations, macrolactonizations, and macrolactamizations

Fragmentation Reactions



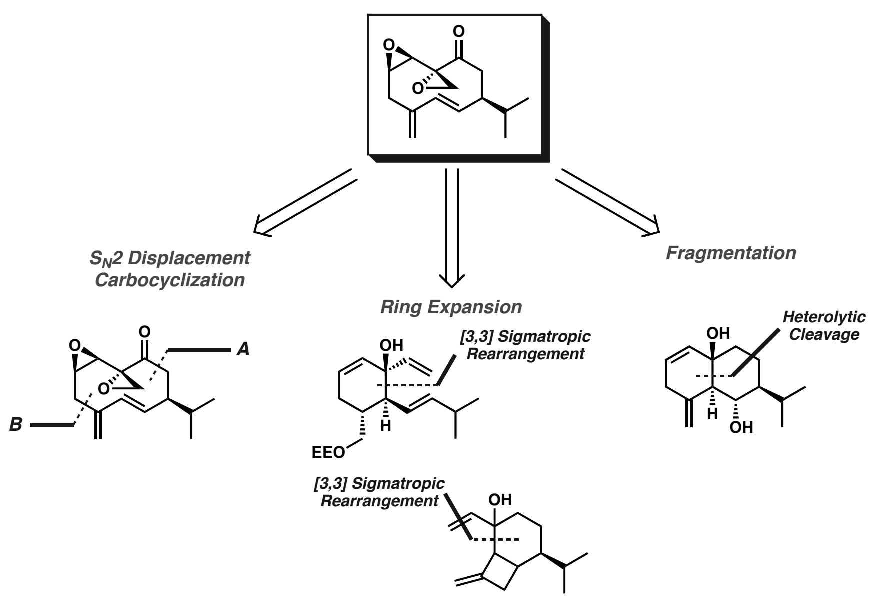
including ionic and radical processes

Ring Expansion (and Contraction) Reactions

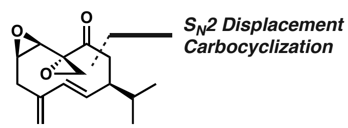


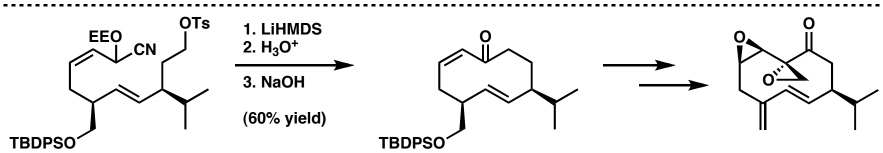
including pericyclic methods

Periplanone B



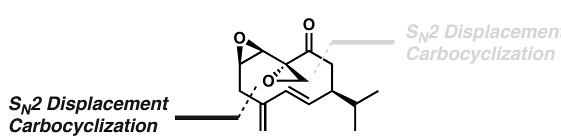
Periplanone B



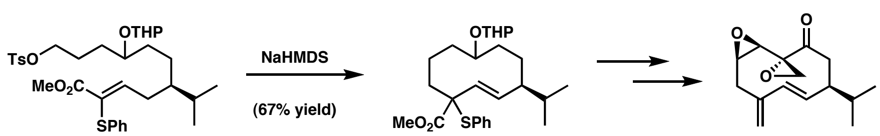


Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. *J. Org. Chem.* **1986**, *51*, 3393-3394.

Periplanone B

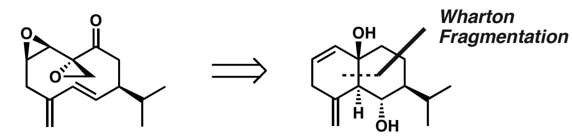


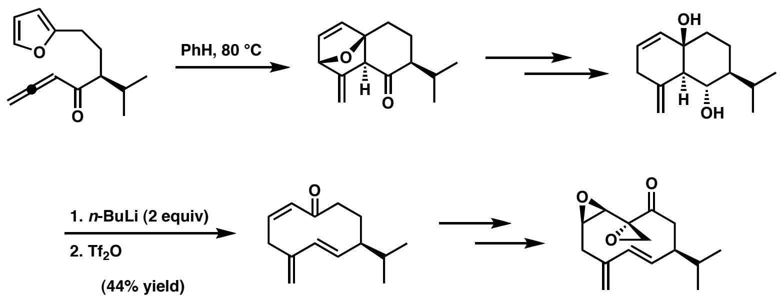
Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. *J. Org. Chem.* **1986**, *51*, 3393-3394.



Kitahara, T.; Mori, M.; Mori, K. *Tetrahedron* **1987**, *43*, 2689-2699.

Periplanone B





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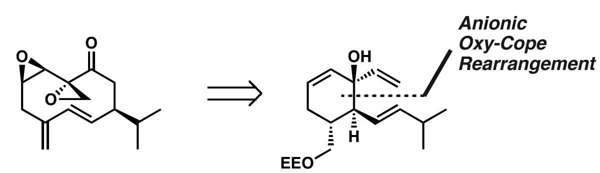
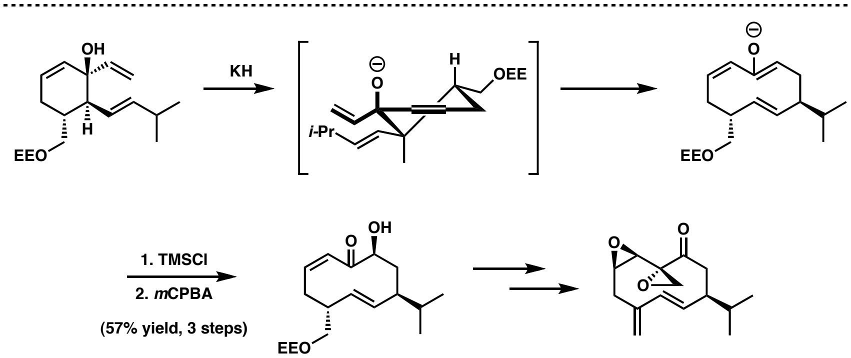
Periplanone B





Intermediate advanced to 4 different diastereomers of periplanone B

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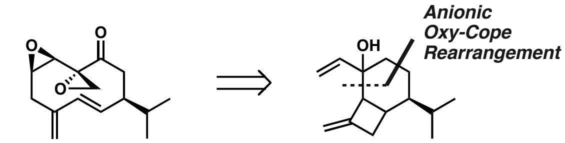
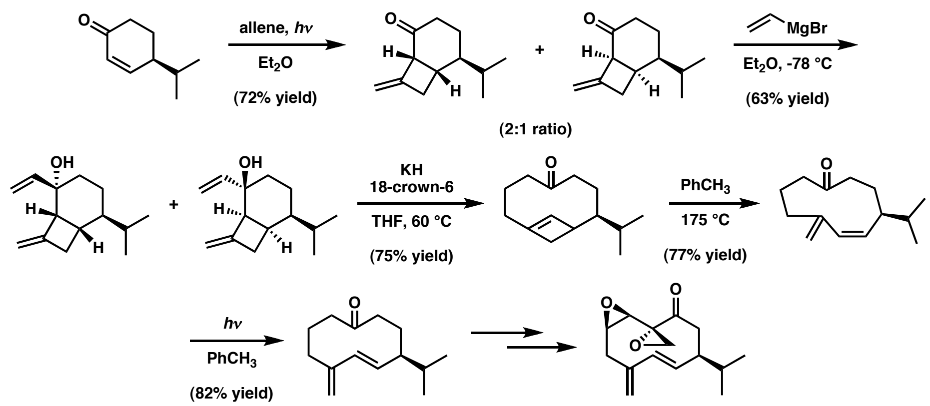
Periplanone B





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Conclusions